REMARKS

By an Office Action dated August 18, 2005 in the file of the above-identified application the Examiner persevered in the requirement for restriction, objected to the specification, rejected certain claims of the application for indefiniteness and rejected all the claims of the application based on prior art. The applicants above have made minor changes to the claims and present comments herein in which the merits of the Examiner's rejection are discussed. Based on these amendments and the comments contained herein, reconsideration of the merits of this patent application is respectfully requested.

In the Office Action the Examiner objected to the specification because paragraph [00044] contained references to the Figures but did not specify which Figures. In addition the paragraph makes reference to a table not contained within the application as filed. Those informalities have been cured by changes to the specification made above.

In a first rejection to the claims, the Examiner rejected Claims 2, 8, 11 and 14 under Section 112, second paragraph, for indefiniteness. The applicants claims include language reciting ventricular-like, atrial-like, and nodal-like action potentials, and the Examiner objects to that terminology. The applicants respectfully traverse this rejection.

The type of testing of cardiomyocytes described in this patent application is conventionally done by trained scientists known as electrophysiologists. Electrophysiologists are trained in the techniques of measuring action potentials of cells in general, and of cardiac cells in particular, and are familiar with the profiles of action potentials generated by various types of cardiac cells. Trained electrophysiologists understand the difference between the action potentials created by ventricular cells, atrial cells, and nodal cells. As recited in the specification, the action potentials created by the cardiomyocytes derived from embryonic stem cells described in this patent application still have some of the characteristics of embryonic cells, and thus do not have the exact characteristics of adult cardiomyocytes, whether nodal, atrial, or ventricular. Therefore the language ventricular-like, atrial-like, and nodal-like was used to refer to these embryonic potentials. From the use of the terms in the specification, the terms are both definite and the best wording available to describe the action potentials that are measured. Those of ordinary skill in the art can look at the action potentials achieved in Figures 2, 3 and 4 and recognize those action potentials as characteristic of atrial cells, ventricular cells, or nodal cells, even though those characteristics

do not exactly match the precise profiles which are obtained from adult cardiomyocytes from donated heart tissue. It is believed the standard for indefiniteness is indefiniteness to one or ordinary skill in the art. The applicants here submit that these terms are capable of definite understanding by those of ordinary skill in the art and that the use of these terms is therefore proper. Accordingly, the applicants request that this objection be reconsidered and withdrawn.

As an alternative, if the Examiner requires, the applicants stand ready to remove the language referring to "like" and have the claims read that the action potentials are atrial, ventricular and nodal. However, for the reasons stated above, the applicants submit that the language in the claims as they stand is the better choice.

The first action on the merits in the Office Action was a rejection under Section 102 for Claims 1, 2, 7, 8, 10, 11, 13, and 14 over either of two prior art references, one to Bosch et al. and one to Li et al. The applicants assert that this rejection was not properly applied in the Office Action, but the applicants have also made an amendment to the claims above to make it clear that this rejection is no longer applicable to the claims in this case.

Both Bosch et al. and Li et al. describe conducting electrophysiology experiments with mature cardiomyocytes derived from adult heart tissue. The applicants admit that doing that is known in the prior art. Those heart cells taken from donated heart tissue, however, are not derived from human embryonic stem cells. A fertilized zygote from which a human being develops is not an embryonic stem cell. It is not at all clear that anywhere in the normal development of a human being that in the direct lineage between the zygote and the heart cell of the adult that anywhere there is a human embryonic stem cell in that lineage. Human embryonic stem cells are believed to be an artifact of technical cell culture and may not exist in the developing embryo.

Nevertheless, to avoid the scientific and philosophical discussion of whether or not embryonic stem cells do exist in a human body, a limitation has been added to the claims to make it clear that the cardiomyocytes are derived by *in vitro* culture of human embryonic stem cells. This is a clear difference from this cited prior art, and a very meaningful difference. One of the reasons that the vast majority of studies on heart tissue for drug screening and scientific research are currently done on animal models is that there are not sufficient human cardiomyocytes available to science to screen and test drugs. While

experiments can be done in a limited research settings, as exemplified by the papers to Bosch et al. and Li et al., donated living heart tissue is rarely available for electrophysiology experiments, such as those which are done in connection with drug screening and testing. Accordingly, the ability to make cardiomyocytes from human embryonic stem cells offers the prospect of an unlimited supply of human cardiomyocytes which may be used for drug screening and testing. These claims thus now recite a clear difference from the cited prior art and a non-obvious one. Until the work described here it was not clear that transmembrane action potentials could be created, measured and studied on cardiomyocytes derived from human embryonic stem cells.

Accordingly it is believed that this rejection for anticipation should be reconsidered and withdrawn.

Secondly, on page 8 of the Office Action is a rejection to Claims 1, 2, 10, 11, 13 and 14, also under Section 102, by a patent application by Gepstein et al. which resulted in a published patent application. The applicants respectfully traverse this rejection as well. The patent application to Gepstein et al does not show the measurement of transmembrane action potential of a cardiomyocyte and does not show that the duration of that transmembrane action potential can be altered by an agent and that alteration measured by electrophysiology equipment. This is a critical difference.

In the patent application to Gepstein et al., there are electrical measurements of the cells, but these electrical measurements are not transmembrane measurements. In fact, the Gepstein et al. application makes it very clear that only extracellular measurements of cardiomyocytes in their culture medium are taken. The difference is real and important. A comparable external electrical heart activity measurement is a surface electrocardiogram on a patient, which shows averaged electrical impulses from the entire heart muscle. A surface EKG cannot provide a clear definition of the electrical activity of single heart cells, something which can only be provided by cellular electrophysiology methods.

One of the main reasons to test potential drugs on human cardiomyocytes is to determine if the human drugs block or alter the functional properties any of the specific ion channel proteins contained within a human heart cell or cardiomyocyte. Measuring extracellular voltages does not permit clear determination of whether or not specific ion channels are blocked or provide any way to determine which ion channels are blocked. Nor

do extracellular recordings allow one to discriminate the type or types of heart cells the properties of which are altered by the agent. These properties can only be directly assessed by cellular electrophysiology measurements, such as by inserting an electrode into the interior of the cell and measuring transmembrane voltage and changes in that voltage. The all or none transmembrane voltage electrical spike of a cardiomyocyte is referred to as the transmembrane action potential, as is well known by those electrophysiologists of ordinary skill in the art. The step of measuring transmembrane action potential is specifically claimed in the method claims of this application. It is a measurement taken directly from a signel cell that provides direct information about the electrical properties of that cell rather than a complex indirect measurement of the electrical activity of hundreds of thousands of different cells in culture. The method step of measuring the transmembrane action potential of a single cell is nowhere found in patent application by Gepstein et al. and is not made obvious by that teaching either. Accordingly, it is believed that this 102 rejection is not well founded and should be reconsidered and withdrawn.

It is specifically noted that Gepstein et al. does suggest testing cardiomyocytes with new drugs. However, until one can demonstrate that transmembrane potentials can be achieved in the cardiomyocytes and provides a practical way to obtain transmembrane potentials, that is a theory only and not a practical reality. In addition, without measurement of transmembrane action potential, it is not possible to determine unambiguously which properties of the action potential or the possible ion channels that are being affected by the drug candidate. The applicants here have demonstrated that it can be done and have demonstrated a method by which it can be accomplished. Thus Gepstein et al. does not make the method of the present invention obvious and certainly does not anticipate these claims.

Lastly, claims stand rejected under 103 for obviousness based on the same references discussed above. And also in view of a reference to Carlsson et al.

All of the comments made above with regard to the Bosch et al., Li et al., and Gepstein et al. references are equally applicable to this rejection. None of the cited prior art teaches that the actual transmembrane electrophysiology of human cardiomyocytes made in culture from embryonic stem cells can be obtained and that such measurements can be tracked during drug studies to see if the ion channels of the cardiomyocytes are affected by

agents in the medium. The applicants have done that and that is not demonstrated in any of the prior art cited by the Examiner, whether taken singly or collectively.

In the second rejection under 103, the Examiner seeks to combine the teaching to Carlsson et al. with that of Gepstein et al. This rejection also merits specific comment by the applicants since the applicants believe this rejection is also not properly supported. It is true that Carlsson shows that transmembrane action potentials can be measured and tracked to determine the effect of drugs on the transmembrane action potentials. Gepstein et al. also shows that cardiomyocytes can be made from human embryonic cells. This observation, by the way, is not unique to Gepstein et al. From the initial culture of human embryonic stem cells, it was early demonstrated that embryoid bodies cultured from human embryonic stem cells would spontaneously beat, thereby demonstrating that cardiac cells were spontaneously created by human embryonic stem cells grown into embryonic bodies. Making cardiac cells from human embryonic stem cells is not new in this patent application and was not new to Gepstein et al.

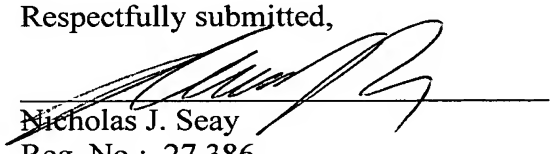
What was not evident before the work describe here, and what is not evident from the teachings either of the Carlsson et al. reference or the Gepstein et al. published patent application, is that cardiomyocytes derived from human embryonic stem cells could be located and pierced by electrophysiology apparatus and the transmembrane potential of those cells could be measured, monitored and followed as drug candidates are applied into the medium in which the cardiomyocytes were cultured. The applicants have demonstrated that known ion channel blocking agents can be detected by the method described here. The applicants here have demonstrated for the first time that all three basic cell types of the human heart, nodal, ventricular, and atrial, cells can be found in the population of cardiomyocytes made by the methods described here, and that is also not demonstrated in the prior art. Again, as noted above, the action potentials are referred to as atrial-like, ventricular-like and nodal-like only because the cells do not match exactly the characteristics action potentials of adult cells of each of the three types. However, the achievement of this result demonstrates the utility of cardiomyocytes derived from human embryonic stem cells for cardiac drug screening and testing in a way not found in Carlsson et al. which only showed extracellular measurements. The reason that the Carlsson et al. teaching is defective is because it also only provides an extracellular measurement of the electrical activity of

many cells to produce a monophasic action potential which does not provide the precise information content available in the measurement of single cellular action potentials. Furthermore, theoretically combining the technique of Carlsson et al. with the cells described by Gepstein et al would not overcome the limitation of multiple different cells types included in the averaged electrical signal which cannot be extrapolated to the precise underlying cellular electrophysiology properties. Accordingly, the combination of these two references not does make obvious the method described in the claims of the present patent application, since it was not obvious from these references, even if taken together, that the methods described by the applicants here would actually work.

Accordingly, it is believed by the applicants that the rejections applied against the claims of this application should be reconsidered and withdrawn.

A separate petition for extension of time is submitted herewith so that this response will be considered as timely filed. Please charge the fee to Deposit Account No. 17-0055.

Respectfully submitted,



Nicholas J. Seay
Reg. No.: 27,386
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701

TEL 608/251-5000
FAX 608/251-9166